Green oxidation with aqueous hydrogen peroxide

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Aqueous H_2O_2 is an ideal oxidant, when coupled with a tungstate complex and a quaternary ammonium hydrogensulfate as an acidic phase-transfer catalyst. It oxidizes alcohols, olefins, and sulfides under organic solvent- and halide-free conditions in an economically, technically, and environmentally satisfying manner.

Introduction

"Green Chemistry" is a central issue, in both academia and industry, with regard to chemical synthesis in the 21st century.[1] Without this approach, industrial chemistry is not sustainable. Chemists are proud of their ability to create highly valuable compounds from inexpensive raw materials. Our health and daily life rely on man-made substances such as pharmaceuticals, fine chemicals, synthetic fibers, and plastics which are

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produced by multi-step chemical conversions of petroleum- or biomass-based feedstocks. However, the current standards of chemical synthesis need to be much improved. Many existing chemical processes, though beneficial, produce unwanted wastes along with target products, and inefficient recovery of solvents is an environmental problem.[2] Thus, the development of environmentally benign and clean synthetic technology is a goal of research and industry. Every reaction should proceed with a high atom-economy,[3] and the overall synthesis must be accomplished with a low E-factor,[4] thereby minimizing the cost of waste disposal.

Oxidation is a core technology for converting petroleum-based materials to useful chemicals of a higher oxidation state. However, oxidation is among the most problematic processes. Many textbook oxidation methods are unacceptable for practical synthesis; the heavy metal oxidants form toxic wastes, while known organic stoichiometric oxidants are usually very expensive.[5] Nitric acid, the most conventional industrial oxidant,[6] is cheap but unavoidably forms various nitrogen oxides. Thus, there is a need for the invention of clean, safe oxidation procedures. Molecular oxygen is obviously an ideal oxidant,[7] but aerobic oxidation is often difficult to control and sometimes results in combustion and the reaction is performed with a low conversion to avoid over-oxidation. Furthermore, although both oxygen atoms in O_2 may be utilized for oxidation (100% atom efficiency),[8,9] only one oxygen atom has been used in most reactions (50% atom efficiency),[10] so the oxidation often requires certain reducing agents to capture the extra oxygen atom during the reaction.[11] In some cases, the initial oxidation products such as (hydro)peroxides are reduced to obtain the desired products.

Hydrogen peroxide, H_2O_2, is a very attractive oxidant for liquid-phase reactions.[12] H_2O_2 is an adduct of H_2 and O_2 that is also viewed as an adduct of an O atom and an H_2O molecule. It can oxidize organic compounds with an atom efficiency of 47% and with the generation of water as the only theoretical co-product. It is relatively cheap, < 0.7 US dollar kg^{-1} (100% H_2O_2), and about 2.4 million metric tons are produced for use, mainly as bleach.[13] It should be noted that H_2O_2 can be an ideal, waste-avoiding oxidant only when it is used in a controlled manner without organic solvents and other toxic compounds. Thus, the discovery of an efficient catalyst and the choice of reaction conditions are the keys to realizing an ideal oxidation procedure. The reaction should be achieved with an H_2O_2 concentration of $< 60\%$, because the use, storage, and transportation of higher concentrations of H_2O_2 are not desirable for safety reasons.[14] The H_2O_2 oxidation is particularly useful for the synthesis of high-value fine chemicals, pharmaceuticals or agrochemicals, and electronic materials which require high chemical purity. It may also be used for improving the environment by oxidative removal of very small amounts of

toxic compounds. However, despite a sustained effort in industry, the current cost of H_2O_2 still does not allow for the economical production of inexpensive compounds in large quantities. There will be significant changes depending on the development of low cost H_2O_2 production, demand for high product quality, stringent environmental regulations, changes in public opinion, legislation, and taxation policy regarding environment protection. In fact, there is a trend to use H_2O_2 as an oxidant for large volume processes such as caprolactam synthesis (Sumitomo Chemical Co.)[15] and propylene oxidation (BASF and Dow Chemical Co.).[16] H_2O_2 oxidation methods may switch to *in situ* or on-site technology using H_2 and O_2. Since the structures of chemical substances are diverse and reaction volumes variable depending on whether the purpose is research or production, no synthetic methods can be universal. One of the major advantages of the H_2O_2 oxidation is the high tunability of the reaction parameters. We foresee that H_2O_2 and O_2 (or air) will be complementary useful clean oxidants in practical chemical synthesis.

Here we describe the oxidation of various organic compounds using H_2O_2, a physiologically harmless tungstate catalyst,[17] and a phase-transfer catalyst (PTC)[18] which proceeds safely without organic solvents and halides. The tungstate complex serves as an excellent precatalyst, because it does not cause unproductive decomposition of H_2O_2. H_2O_2 oxidation was initiated by Payne[19] (alcohol oxidation) and Jacobson[20] (olefin epoxidation), developed largely by Venturello[21] and Ishii[22] among others,[23,24] and studied mechanistically by Aubry,[25] Griffith,[26] and Hill.[27] Our recent work has overcome many of the serious problems that have plagued this significant subject of chemistry.

Oxidation of alcohols

Oxidation of alcohols to carbonyl compounds is a fundamental procedure in synthetic organic chemistry.[28] We found that a combined system of sodium tungstate (Na_2WO_4) and methyltrioctylammonium hydrogensulfate [$CH_3(n\text{-}C_8H_{17})_3N^+HSO_4^-$ ($Q^+HSO_4^-$)] as a PTC catalyzes efficiently the dehydrogenation of alcohols with 30% H_2O_2 to give the corresponding carbonyl compounds in high yields.[29] The reaction is run at or below 90 °C (for safety reasons) without using hazardous organic solvents. Only a slight excess of H_2O_2 is necessary, because unproductive decomposition is negligible.

Typically, oxidation of 100 g of 2-octanol was effected by using 96 g of 30% H_2O_2, 0.5 g of $Na_2WO_4 \cdot 2H_2O$, and 0.7 g of $Q^+HSO_4^-$ with a catalyst to substrate (S/C) molar ratio of 500 and stirring vigorously at 90 °C for 4 h to give 2-octanone in a near quantitative yield.[29] The pure ketonic product (93.9 g, 95% yield) was obtained simply by separation from the aqueous phase, washing with saturated $Na_2S_2O_3$, and distillation.

The oxidation proceeds in an organic–aqueous biphasic system. Without the quaternary ammonium salt as a PTC, the yield of 2-octanone was <1%. The combination of the lipophilic Q cation (Q refers to $CH_3(n\text{-}C_8H_{17})_3N$ throughout this paper) and the HSO_4 anion is important. Use of Q chloride or *N*-hexadecylpyridinium chloride gave the ketone in only 11 and 7% yield, respectively. These conventional chloride PTCs have been used only in chlorinated hydrocarbons such as 1,2-dichloroethane,[23f] while this new procedure using $Q^+HSO_4^-$ does not require organic solvents. The yield of the standard reaction using $Q^+HSO_4^-$ was lowered to 59% by the addition of 5 equiv. of NaCl to the PTC.[30] The reaction of 2-octanol with an S/C ratio of 200,000 (alcohol : H_2O_2 : Na_2WO_4 : $Q^+HSO_4^-$ = 200,000 : 300,000 : 1 : 100) gave a turnover number (TON, defined as mol product per mol catalyst) of 77,000 (40% yield). This value is two orders of magnitude higher than any previously reported H_2O_2 oxidation.

In a similar manner, oxidation of 1-phenylethanol with S/C = 400,000 gave an even higher TON of 179,000.

Fig. 1 shows examples of the solvent-free oxidation achieved on a 100-g scale and with S/C = 500. Various secondary
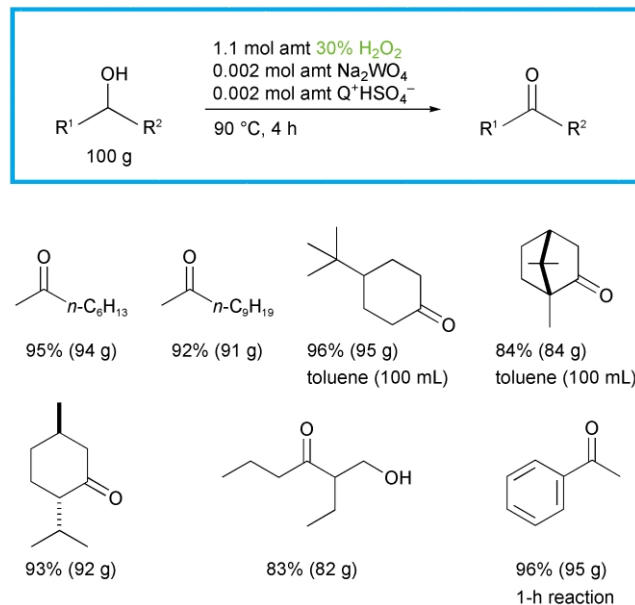

Fig. 1 Oxidation of secondary alcohols to ketones.

alcohols are converted to ketones in high yields. Both *cis*- and *trans*-4-*tert*-butylcyclohexanol were oxidized at equal rates (Note: chromic acid oxidizes the sterically more congested *cis* alcohol three times faster[31]). If it is appropriate, toluene may be used as solvent, for example with solid isoborneol as substrate. The oxidation of 2-ethylhexane-1,3-diol gave 2-ethyl-1-hydroxy-3-hexanone selectively in 83% yield. 2-Octanol was oxidized without problems in toluene containing aliphatic and aromatic carboxylic esters, dialkyl ethers, epoxides, ketones, or cyanides. Cyclobutanone, initially formed in the oxidation of cyclobutanol, undergoes the Baeyer–Villiger oxidation to give γ-butyrolactone in a moderate yield.[32] Although the reaction of 2-octanol was significantly retarded in the presence of butyramide, *N*-hexyl-6-hydroxyheptamide was oxidized to the keto amide in a high yield. Trityl and *tert*-butyldimethylsilyl ethers are mostly tolerated under such acidic oxidation conditions, allowing for selective oxidation of certain protected polyols. However, the THP group can not be used for protection of primary alcohols. Electron-rich alkoxyaromatic groups tolerate the catalytic conditions.

2-Octanol dissolves 0.50 mmol of H_2O_2 g^{-1} under the reaction conditions. Toluene dissolves 0.0035 and 0.0204 mmol of H_2O_2 mL^{-1} in the absence and presence of 0.006 mM of $Q^+HSO_4^-$, respectively. When $Q^+HSO_4^-$ (0.3 mmol) was stirred with a 1 : 1 mixture of toluene and H_2O (10 mL each) in a 20 mm diameter test tube at room temperature, the acidic PTC was partitioned in the organic and aqueous phase in about a 7 : 3 ratio, and no concentration gradient was seen in either phase. D_2O dissolves 0.068 mmol of the PTC mL^{-1} at 25 °C (^{1}H NMR analysis). Na_2WO_4 is soluble only in the aqueous phase. Thus, this alcohol dehydrogenation occurs under organic–aqueous biphasic conditions.

The mechanism shown in Fig. 2 explains a range of experimental findings in the oxidation.[29] In an aqueous phase, the catalyst precursor Na_2WO_4 is rapidly oxidized by H_2O_2 according to: $Na_2WO_4 + 2H_2O_2 \rightarrow Na_2[WO(O_2)_2(OH)_2] + H_2O$. The resulting bisperoxotungstate compound **A** is in equilibrium with **B** and **C**. The dianion in **A** is feebly active toward alcohols, while the mono- and di-protonated forms in **B** and **C** are sufficiently reactive. Therefore, the catalytic activity
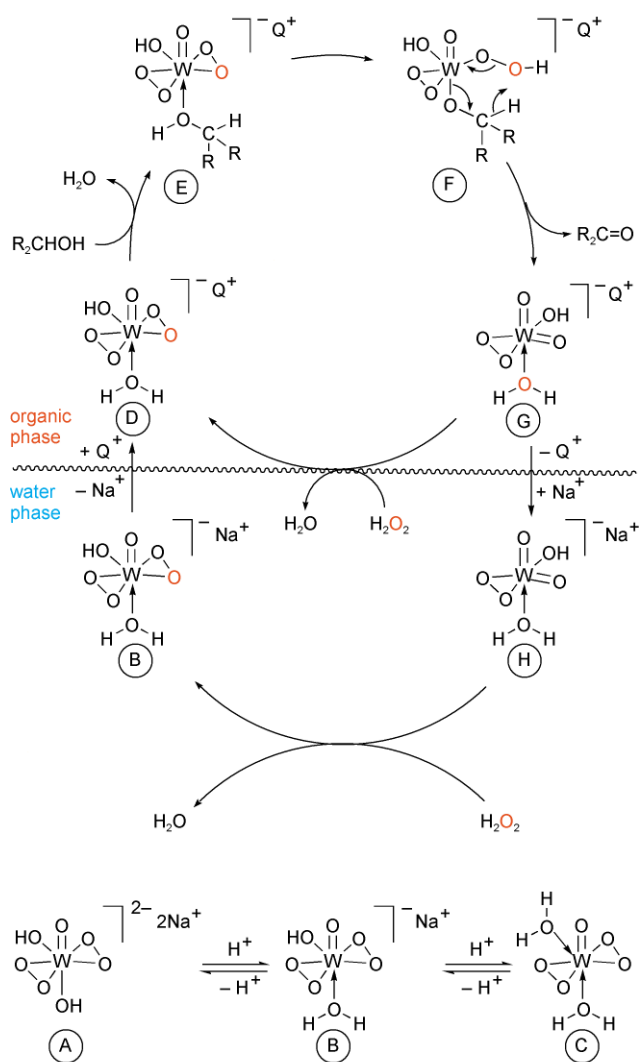
Fig. 2 Catalytic cycle of alcohol oxidation. $Q^+ = CH_3(n\text{-}C_8H_{17})_3N^+$.

is highly dependent on the acidity of the reaction medium as well as the efficiency of aqueous–organic phase transfer of the active species aided by Q^+. In a pH range above 4, the catalytic system that contains largely **A** has only weak oxidative activity even in the presence of Q^+. Since the pK_a value of **C** is 0.1,[33] the mono-protonated species **B** is dominant under reaction conditions with a pH range of 0.4–3, where the HSO_4^- ion is largely deprotonated to SO_4^{2-}. Under such dilute conditions, **B** exists mostly as a monomer.[33,34] Its anion moiety can easily be transferred to an organic phase by Na^+–Q^+ ion exchange. Thus, in the organic layer, the bisperoxo complex **D** undergoes water–alcohol ligand exchange to form **E**. Then proton transfer in **E** generates the reactive species **F**, which forms a ketonic product and **G**. The alkoxy ligand in **F** is dehydrogenated by the adjacent hydroperoxy ligand *via* a six-membered transition state where the hydridic α-hydrogen migrates to the positively polarized oxygen atom. This view is supported by the relative reactivity of *p*-substituted benzyl alcohols ($<10\%$ conversion) showing a ρ value of -0.31. The monoperoxo tungstate ion in **G** is reoxidized by H_2O_2 after returning to the aqueous phase as the ion pair **H**. This step may also occur at an organic–aqueous interface or even in the organic phase to some extent. The neutral bisperoxo compound **C**, present as a minor component, is reactive in a homogeneous phase but unable to move into the organic phase under the biphasic conditions. H_2WO_4, a Na^+-free compound, acts as an excellent precatalyst but only with a PTC because of the operation of the same mechanism in the biphasic system.

The oxidation of secondary alcohols gives ketones, while the reaction of primary alcohols afford carboxylic acids by way of aldehyde intermediates. 1-Octanol is only three-times less reactive than 2-octanol. Various primary alcohols are convertible to carboxylic acids by using a 2.5 molar amount of 30% H_2O_2. Fig. 3 lists examples of the 100-g scale reaction. Simple
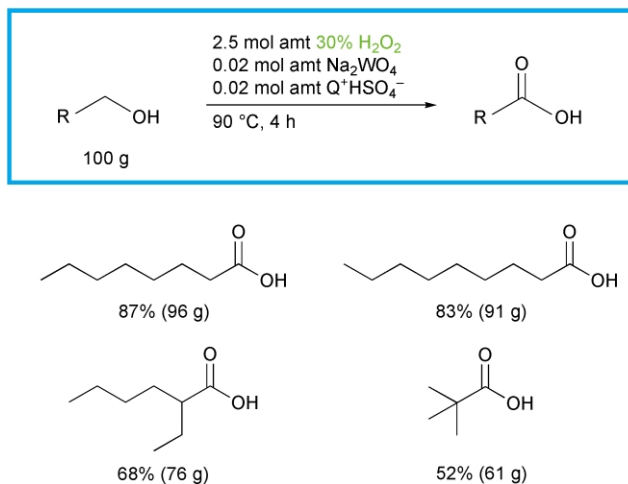

Fig. 3 Oxidation of primary alcohols to carboxylic acids.

primary alcohols gave the best results. 1-Octanol gave octyl octanoate, a dimeric ester, in only 2% yield. β-Branched primary alcohols tend to afford a lower yield. The reaction can not be halted at the stage of an aldehyde due to the rapid oxidation that takes place *via* the hydrate and, more probably, peroxy hydrate. A range of benzylic alcohols can be oxidized directly to the benzoic acids using a 2.5–5 molar amounts of H_2O_2 (2 molar amount in theory) and with an S/C ratio of 100. Some examples are given in Fig. 4.
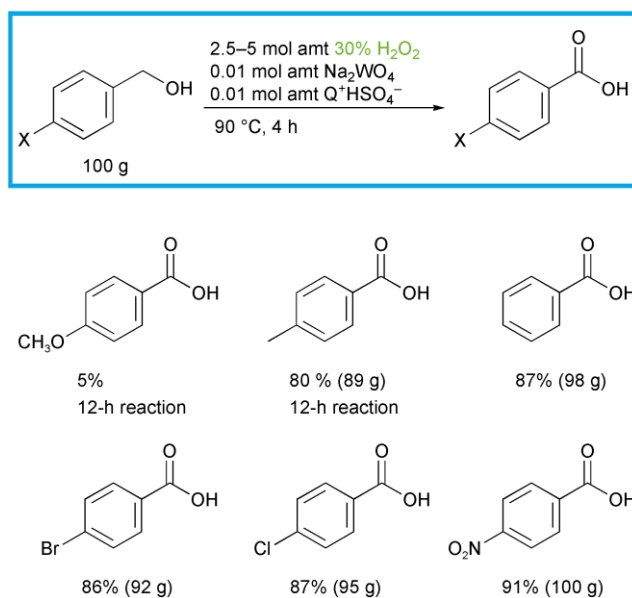

Fig. 4 Oxidation of benzylic alcohols to benzoic acids.

Fig. 5 illustrates the pathways of oxidation of primary alcohols. The preferred pathway is highly dependent on the structures and reaction parameters. The peroxy hydrate intermediate undergoes 1,2-hydride migration accompanied by dehydration. In going from the straight-chain to β-branched alkanol, the extent of the alkyl migration is enhanced relative to the desired hydride migration, lowering the yield. This pathway results in the loss of one carbon and the alcoholic product undergoes further oxidation. For the same reason, *p*-methox-
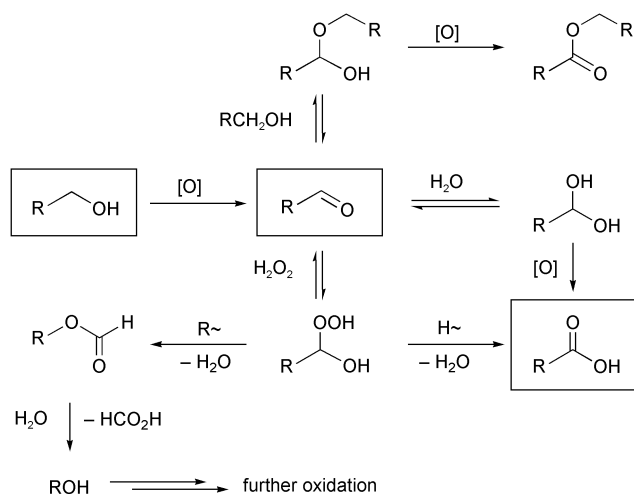
Fig. 5 Pathways of oxidation of primary alcohols.

Fig. 7 Chemoselective oxidation of olefinic alcohols.

ybenzyl alcohol is not convertible to the benzoic acid, where the phenolic product gives complicated oxidation products.

By selecting suitable reaction conditions, benzylic alcohols, unlike simple alkanols, are oxidized to benzaldehydes where the efficiency is highly dependent on the electronic properties of the substituents. Unsubstituted benzyl alcohol can be selectively converted to benzaldehyde or benzoic acid, simply by changing the amount of H_2O_2. As expected, various arylcarbinols possessing an electron-donating substituent were oxidized to the corresponding aldehydes in good yields. Fig. 6 illustrates
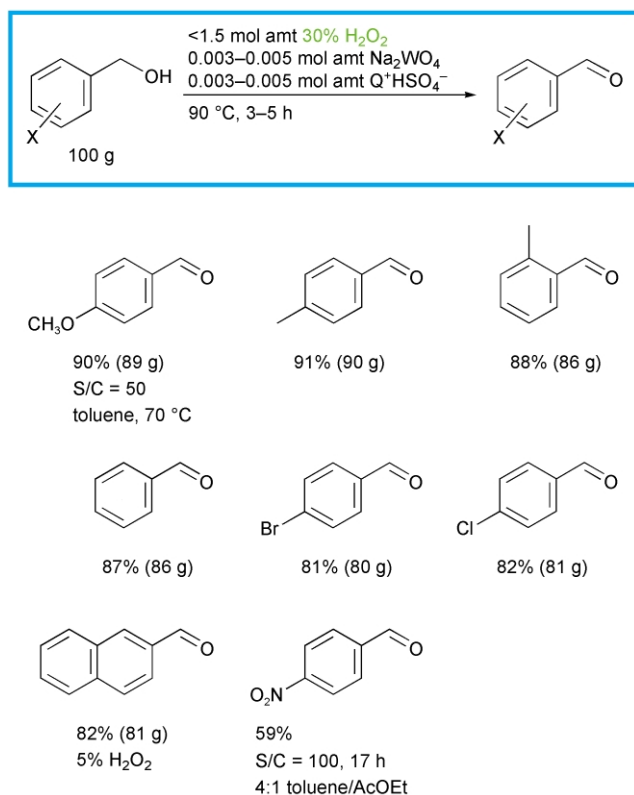
Fig. 6 Oxidation of arylcarbinols to aldehydes.

examples of the reaction achieved on a 100-g scale using a < 1.5 molar amount of H_2O_2 and an S/C ratio of 50–330 : 1. *p*-Methoxybenzyl alcohol was an excellent substrate, whereas *p*-nitrobenzyl alcohol gave the aldehyde in only 59% yield.

Alcohol/olefin chemoselectivity is a major concern in oxidation chemistry (Fig. 7). Oxidation of 11-dodecen-2-ol, a model substrate possessing both hydroxyl and olefinic func-
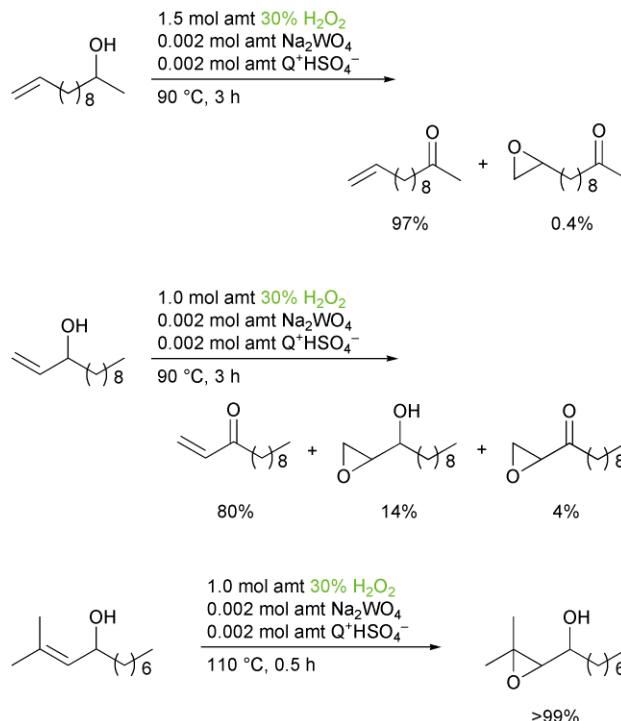
tional groups, gave 11-docecen-2-one in 97% yield together with only 0.4% of 11,12-epoxydodecan-2-one. However, selective dehydrogenation of allylic alcohols is difficult because of the easy epoxidation.[5,9] 1-Dodecen-3-ol, an allylic alcohol with a terminal olefinic bond, was converted to the desired 1-dodecen-3-one in 80% yield, contaminated with 1,2-epoxydodecan-3-ol and 1,2-epoxydodecan-3-one in 14% and 4% yields, respectively. However, 2-methyl-2-undecen-4-ol with a trisubstituted olefinic bond underwent selective epoxidation in > 99% yield. Notably, geraniol and cinnamyl alcohol are oxidized to citral and cinnamaldehyde in 97 and 96% yields, respectively, by reaction with a 1.1 molar amount of 5% H_2O_2 and reusable Pt black as catalyst (S/C = 33, 90 °C, 5 h) without organic solvent.[35] (*E*)-3-Octen-2-ol was converted to 3-octen-2-one in 97% yield under similar conditions.

This solvent- and halide-free oxidation of alcohols has been used at Creighton University to demonstrate green chemistry to students.[36]

Oxidation of aldehydes to carboxylic acids

Aqueous H_2O_2 has been considered to have only a weak ability to oxidize aldehydes to carboxylic acids.[37] However, during this investigation, we discovered that the oxidation proceeds under aqueous–organic biphasic conditions without any organic solvents, halides, or metal catalysts.[38] For example, reaction of 100 g of octanal, 133 g of 30% H_2O_2, and 1.82 g of $Q^+HSO_4^-$ (200 : 300 : 1 molar ratio) at 90 °C for 2 h with magnetic stirring at 1000 rpm, followed by workup and distillation gave 91.5 g of octanoic acid (81% isolated yield; 85% by ^{1}H NMR analysis). The use of a lipophilic, acidic Q salt as catalyst is the key to the efficient biphasic oxidation. As shown in Fig. 5, the reaction takes place *via* perhydrate intermediates, where the acidic Q salt facilitates the addition of H_2O_2 to aldehydes in the organic layer and, more importantly, the elimination of water from the tetrahedral intermediate.

This is a simple, clean oxidation procedure suitable for medium- to large-scale synthesis. Some examples are given in Fig. 8. The W catalyst is unnecessary. Its utility is limited by the structural characteristics for mechanistic reasons (Fig. 5); straight-chain alkanals and benzaldehydes with an electron-
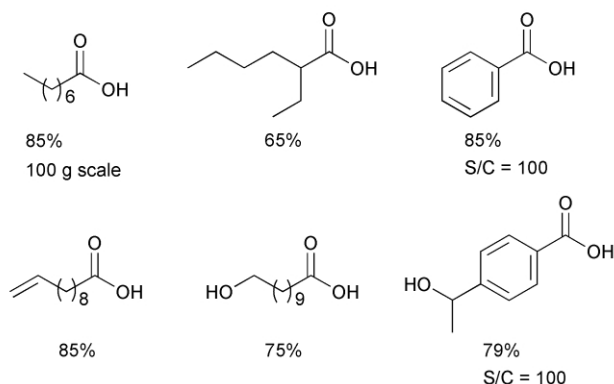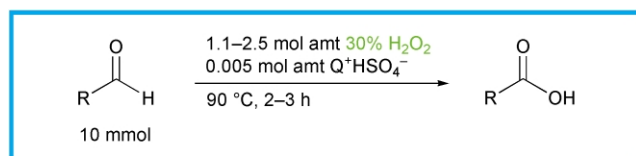
Fig. 8 Solvent- and metal-free oxidation of aldehydes.

Fig. 9 Epoxidation of simple olefins.

withdrawing substituent are good substrates. Notably, because of the absence of metallic catalysts, alcoholic (primary and secondary) and olefinic functions survive the oxidation conditions.

Epoxidation of olefins

A clean epoxidation method is needed in modern organic synthesis.[39] In particular, a practical procedure for terminal olefins has been elusive. We first searched for conditions to epoxidize olefins with 30% H_2O_2 without an organic solvent and any halides. We found that a ternary system consisting of Na_2WO_4, (aminomethyl)phosphonic acid, and $Q^+HSO_4^-$ generally catalyzes epoxidation of simple olefins with a consistently high yield.[40] The addition of (aminomethyl)phosphonic acid is crucial for catalytic activity toward olefinic substrates. Reaction of 100 g of 1-dodecene, known as the least reactive olefin, proceeded smoothly by using a 1.5 molar amount of 30% H_2O_2 (olefin : H_2O_2 : Na_2WO_4:$Q^+HSO_4^-$: phosphonic acid = 100 : 150 : 2 : 1 : 1) and with stirring at 1000 rpm at 90 °C for 2 h to afford 96.2 g (87% yield) of 1,2-epoxydodecane after distillation of the organic phase.

As listed in Fig. 9, various olefins were epoxidized on a 100-g scale by the two-phase reaction. Toluene may be used as the cosolvent, if it is more appropriate. This procedure is cost-effective. Furthermore, many otherwise unreactive terminal olefins are usable. Internal olefins are more reactive, giving the epoxy products in a high yield. The epoxidation of 1,2-disubstituted olefins proceeds stereospecifically with retention of the configuration, as exemplified by reaction of (Z)- and (E)-3-octene. Competitive experiments show the following relative reactivities: 1-octene (1), (E)-3-octene (1.9), (Z)-3-octene (14), 2-methyl-1-undecene (2.1, 1,1-disubstituted olefin), 2-methyl-2-nonene (4.0, trisubstituted olefin), and 3,4-diethyl-3-hexene (5.8, tetrasubstituted olefin). Since the oxidizing species is electrophilic, the reaction rate is enhanced with increasing electron density of the olefinic bond.[41] However, the extent of structural sensitivity is rather moderate. Notably, (Z)-3-octene is more reactive than the E isomer by a factor of 7.3, as observed in epoxidation with dimethyldioxirane[42] (3-hexene, Z/E = 8.3) and a special peroxycarboxylic acid[43] (2-octene, Z/E = 7.7) (cf. 1.2 with m-chloroperbenzoic acid). The Z-preference is more apparent with β-methylstyrene giving Z/E > 27. Cyclooctene is particularly reactive. The catalyst system displays a TON as high as 150–450 per W atom with terminal olefins and 1600 with cyclooctene. Reaction in the absence of (aminomethyl)-
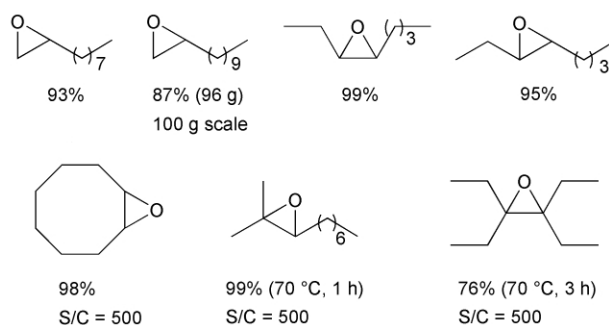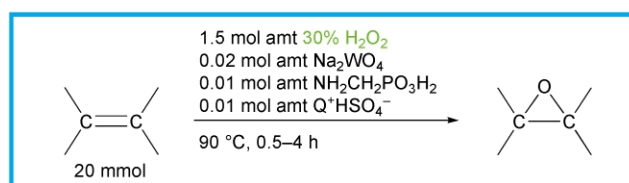
phosphonic acid shows the following relative reactivities: 1-octene (1), (E)-3-octene (2.8), (Z)-3-octene (4.2, Z/E reactivity = 1.5), 2-methyl-1-undecene (2.6), 2-methyl-2-nonene (3.6), and 3,4-diethyl-3-hexene (3.1), suggesting a change in the reactive intermediate.

The substrates of the biphasic H_2O_2 epoxidation are not limited to simple olefins. Olefins containing an ester, ether, or α,β-enone linkage in the same molecule can be epoxidized by this procedure, as illustrated in Fig. 10. Styrene is inappropriate
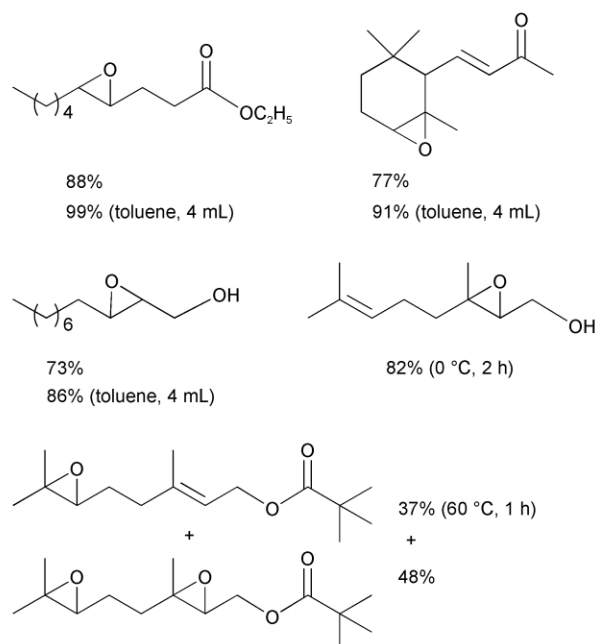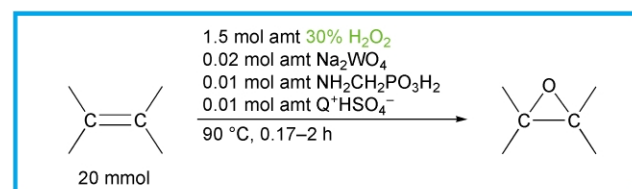

Fig. 10 Epoxidation of functionalized olefins.

as a substrate, because the epoxy product is highly sensitive to acid-catalyzed hydrolysis.[44] Introduction of a lipophilic group at the *para* position increases the yield to some extent. Allylic

alcohols are very reactive. Geraniol is oxidized rapidly even at 0 °C to give only C(2)–C(3) epoxide. In contrast, the reaction of the pivalate requires heating at 60 °C and epoxidizes mainly at the C(6)–C(7) double bond, the initial C(6)–C(7)/C(2)–C(3) selectivity being *ca.* 3.2 : 1. A different selectivity profile is seen with non-allylic unsaturated alcohols. The epoxidation of 2-cyclohexen-1-ol occurs stereoselectively from the face of the hydroxy function (*syn* : *anti* = 9 : 1), while the pivalate exhibited an opposite diastereoselection (*syn* : *anti* = 1 : 12). The relative reactivity of 2-cyclohexen-1-ol, cyclohexene, and pivalate of 2-cyclohexene-1-ol is 170 : 1 : 0.05. (Aminomethyl)-phosphonic acid enhances the rate of epoxidation of 1-octene by a factor of 31, while the additive slightly retards the 2-octanol dehydrogenation (relative rate 0.8). Thus, addition of (aminomethyl)phosphonic acid changes the relative reactivity of 1-octene and 2-octanol from 1 : 28 to 1 : 5, but terminal olefins are still less reactive than secondary alcohols.

Without (aminomethyl)phosphonic acid, the Na_2WO_4/$Q^+HSO_4^-$ catalyst system epoxidizes 1-octene only very slowly, giving the epoxide in <5% yield after 2 h at 90 °C. Phenylphosphonic acid, and even phosphoric acid, can be used as an accelerator. (Aminomethyl)phosphonic acid is largely (*ca.* 60%) decomposed to phosphoric acid during the epoxidation but is more effective than phosphoric acid. Although the marked effect of the acid additives remains to be elucidated, we consider that the biphasic epoxidation takes place by the cycle illustrated in Fig. 11.[40] The coordination of a phosphonate or phosphate
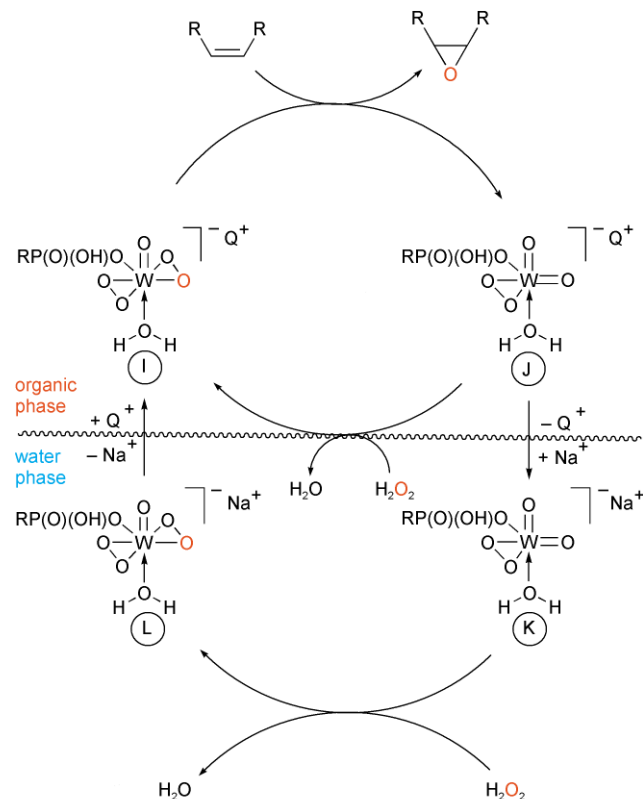

Fig. 11 Catalytic cycle of epoxidation. $Q^+ = CH_3(n\text{-}C_8H_{17})_3N^+$.

anion to the W center increases the electrophilic nature of the peroxo moiety in **I** (aggregation state unknown). The spiro-structured TS **M** (Fig. 12) explains the high reactivity of *Z* olefins relative to the *E* isomers, which is also seen in epoxidation with structurally analogous dimethyldioxirane.[42] Epoxidation can also occur after proton transfer followed by ring opening *via* TS **N**, particularly in the absence of an acid additive. This pathway would show a low *Z* preference like in the reaction with *m*-chloroperbenzoic acid. The hydroperoxy
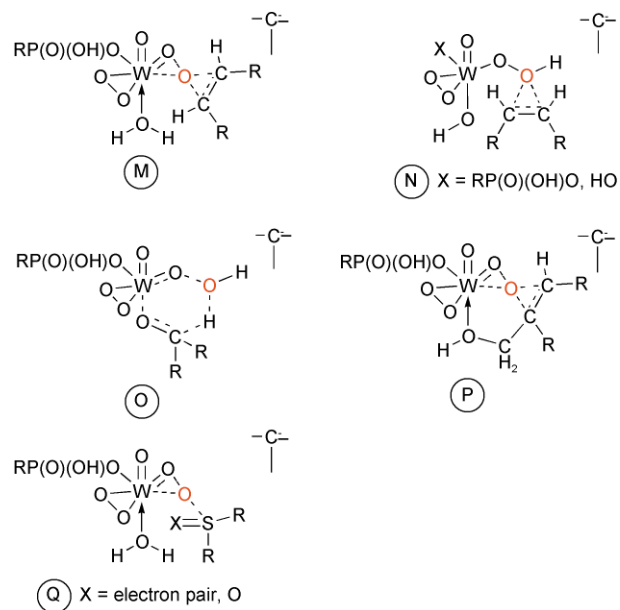

Fig. 12 Possible transition state structures.

compound also dehydrogenates primary and secondary alcohols *via* the six-membered TS **O** (*cf.* Fig. 2). With allylic alcohols, the hydroxy and olefinic bonds are linked by a methylene unit, facilitating the epoxidation *via* TS **P**.

The attractive properties of aqueous H_2O_2 prompted the development of a number of homogeneous and heterogeneous catalyst systems as well as reaction conditions, in addition to our biphasic epoxidation method. In the presence of Nafion NR50 (a resin-sulfonic acid, S/C = 25) but without any metal catalysts, various olefins can be oxidized with a 2 molar amount of 30% H_2O_2 at 70 °C to give the corresponding 1,2-diols in a good yield.[45] Cyclohexene is oxidized to the *trans* diol in 98% yield. The initial epoxidation occurs by an *in situ* formed resin-peroxysulfonic acid. The recovered Nafion resin can be used repeatedly, at least ten times, without losing its catalytic activity.

Direct oxidation of cyclohexene to adipic acid

The utility of this biphasic oxidation method was highlighted by its application to adipic acid synthesis. As shown in Fig. 13,
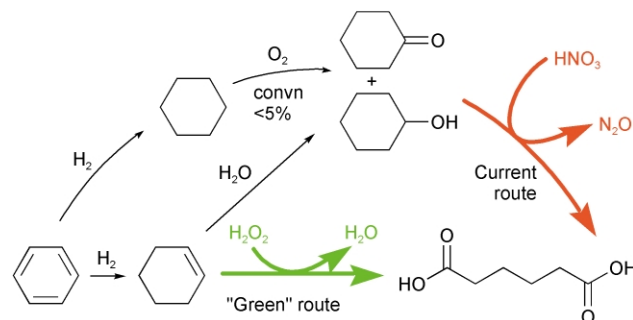

Fig. 13 Synthesis of adipic acid.

currently most industrial production of adipic acid uses nitric acid oxidation of cyclohexanol or a cyclohexanol–cyclohexanone mixture which is accessible from benzene.[46] This technology allows for the worldwide production of up to 2.3 million metric tons per year largely for the manufacture of nylon-6,6, which is used in carpet fibers, upholstery, tire reinforcements, auto parts, and apparel, among others.[46,47] However, this process produces an inevitable stoichiometric waste, nitrous oxide (N_2O),[47] that is commonly thought to cause global warming and ozone depletion.[48] Thus, 400,000 metric

tons of N_2O have been emitted each year. Most adipic acid producers employ a thermal decomposition process with or without catalysts,[49] achieving a diminishment of about 80% in N_2O emission.[50] N_2O can be recovered and its decomposition heat is reusable, however, a huge amount of energy is required for such high-temperature processes.[50] Thus, an environmentally benign practical procedure for adipic acid production is very desirable.[51]

We noticed the excellent technology for the selective hydrogenation of benzene to cyclohexene established by the Asahi Chemical Industry Co.[52] Cyclohexene is a very attractive C_6 starting material and, in fact, is converted to adipic acid similarly *via* cyclohexanol (Fig. 13). We utilized the chemical characteristics of the cycloolefin in a more direct manner. Thus, when a mixture of 100 g of cyclohexene, 607 g of 30% H_2O_2, 4.01 g of $Na_2WO_4 \cdot 2H_2O$, and 5.67 g of $Q^+HSO_4^-$ (olefin : W : PTC = 100 : 1 : 1) was magnetically stirred at 1000 rpm at 75–90 °C for 8 h, 161 g of adipic acid was obtained.[53] Liquid cyclohexene is converted directly to shiny, colorless, analytically pure crystalline adipic acid, as shown in Fig. 14. This direct conversion uses as oxidant only a 4.4 molar amount of H_2O_2 per mol of cyclohexene (4.0 mol in theory). The aqueous phase of the reaction mixture can be reused with a renewed PTC and 30% H_2O_2. This solvent- and halide-free oxidation is clean, safe, and reproducible with conditions that are less corrosive than those of the nitric acid oxidation. No operational problems are foreseen for scaling up the reaction. The practicality of this "green" process depends largely on the cost of H_2O_2 in comparison to nitric acid and the expenses for waste disposal/ recovery, as well as the stringency of restrictions regarding N_2O emission.

As illustrated in Fig. 15, this one-pot transformation is achieved *via* a six-step scheme involving three kinds of oxidative reactions (epoxidation of a cycloolefin, dehydrogenations of two secondary alcohols, and regioselective Baeyer– Villiger oxidation of an α-hydroxy ketone) and two hydrolytic reactions. Many steps in this scheme are facilitated by acidic conditions.

The utility of the tungstate-catalyzed oxidative cleavage of cyclic olefins is demonstrated in Fig. 16.[53] Cyclohexene-4,5-dicarboxylic anhydride (100 g) was converted to crystalline *meso*-1,2,3,4-butanetetracarboxylic acid (141 g, 91% yield). Reaction of cyclopentene (100 g) directly gave crystalline glutalic acid (175 g, 90% yield). Cyclooctene and 1-octene afforded suberic acid and heptanoic acid in only 9 and 36% yields, respectively, since the intermediary epoxides are resistant to acid-catalyzed hydrolysis.[21d]

The adipic acid synthesis has been slightly modified at Oregon University,[54] Monash University,[55] and Tohoku University[56] and used to illustrate the significance of green chemistry to students. $Q^+HSO_4^-$ may be replaced by oxalic acid[57] or sulfosalycylic acid.[58] The oxidation can also be effected by 60% H_2O_2 and H_2WO_4.[59] In a similar manner, 100 g of cyclohexanol is converted to 127 g (87%) of adipic acid by reaction with 498 g (4.4 molar amount) of 30% H_2O_2 and H_2WO_4 (S/C = 100) at 90 °C for 20 h.[60] Cyclohexanone is likewise oxidized to adipic acid in 91% yield by using a 3.3 molar amount of 30% H_2O_2 and H_2WO_4 (S/C = 100). This ketone to dicarboxylic acid conversion is applicable to five- to eight-membered cyclic ketones.

Oxidation of sulfides and sulfoxides

Oxidation of sulfides has a long history.[61] However, most of the earlier methods are unsatisfactory for medium- to large-scale synthesis because of the low atom-efficiency, the formation of environmentally unfavorable wastes, the use of chlorohy-
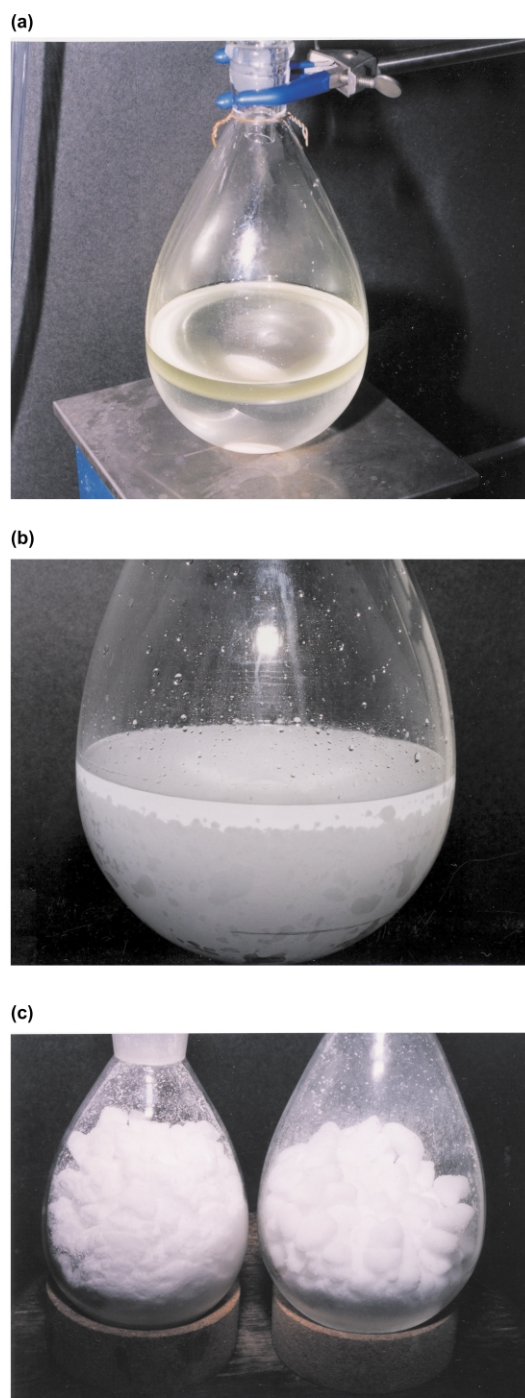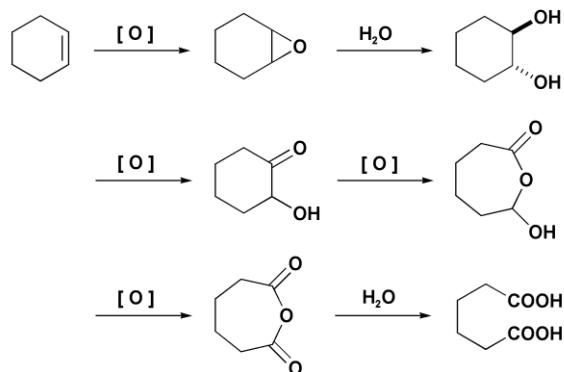
Fig. 14 Direct conversion of cyclohexene to adipic acid. (a) Reaction mixture. (b) Product. (c) Adipic acid product. First run (left) and second run (right).

drocarbon solvents (for metal-catalyzed H_2O_2 oxidation), or the high cost.

We found that aromatic and aliphatic sulfides are oxidized to sulfoxides or sulfones in a high yield with 30% H_2O_2 without organic solvents.[62] The reaction can be conveniently conducted on a large scale and at a low cost. As has been observed with olefin epoxidation, phenylphosphonic acid serves as an excellent promoter of the biphasic oxidation. The reaction is highly productive, giving a TON as high as 122,000 with diphenyl sulfide as substrate. This value is two orders of magnitude higher than the previous best achieved. When 100 g of diphenyl sulfide was subjected to oxidation with 152 g of 30% H_2O_2, 177 mg of $Na_2WO_4 \cdot 2H_2O$, 85 mg of phenyl-
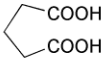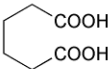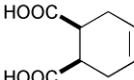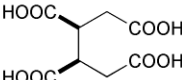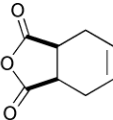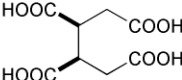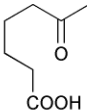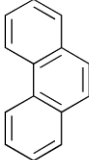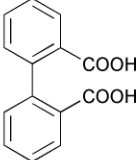
Fig. 15 Direct oxidation of cyclohexene to adipic acid.

Fig. 16 Oxidative cleavage of cycloolefins.

phosphonic acid, and 250 mg of Q+HSO4− (1000 : 2500 : 1 : 1 : 1 molar ratio) with vigorous stirring at 50 °C for 2 h, 112.8 g of diphenyl sulfone (96% yield) was obtained.

Fig. 17 lists some examples. The reaction using a small excess of 30% H_2O_2 takes place smoothly with an S/C of 1000

Fig. 17 Oxidation of sulfides to sulfones.
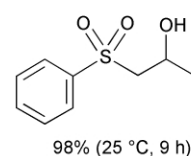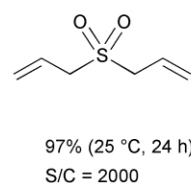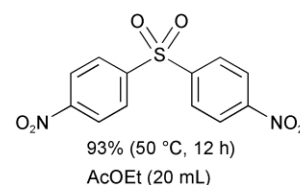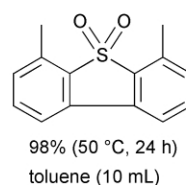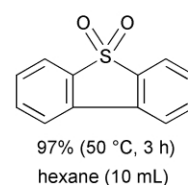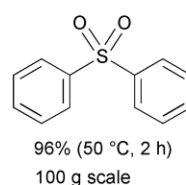
to 5000 at 25–50 °C. Yields are consistently high. Aliphatic sulfides are more reactive than aromatic compounds. The electron-withdrawing nitro group in the phenyl ring or bulky, even two tertiary alkyl substituents, do not affect the synthetic efficiency. Dibenzothiophene, a difficult substrate, can also be oxidized. Under such conditions, the sulfide function is highly reactive. Diallyl sulfide was cleanly converted to diallyl sulfone without epoxidation. Normally reactive trisubstituted olefinic bonds are left intact. Primary and secondary alcohols are unaffected; 2-hydroxyethyl and -hydroxylpropyl phenyl sulfide are oxidized to the sulfones without alcohol dehydrogenation.

We consider that the oxidation proceeds *via* TS **Q** in an organic phase as in olefin epoxidation (Fig. 11 and 12), where the peroxo W complex **I** is highly electrophilic due to the ligation of phenylphosphate. The electrophilicity is much higher than that of H_2O_2. However, unlike olefin epoxidation, neighboring hydroxy functions accelerate the oxidation only slightly.

Dialkyl and alkyl aryl sulfides are cleanly oxidized to sulfoxides at 35 °C using aqueous H_2O_2 without metallic catalysts. Similarly, various tertiary amines and pyridines are convertible to the N-oxides by heating at 60 °C with 30% H_2O_2 containing a resin-sulfonic acid (S/C = 25).[63]

Conclusion

Utilizing aqueous H_2O_2, a series of practical oxidation procedures has been devised, which are suited for medium- to large-scale organic synthesis. A catalytic system consisting of Na_2WO_4 and Q+HSO4− effects the organic–aqueous biphasic oxidation of secondary alcohols to ketones using 30% H_2O_2 without any organic solvents and halides. Certain primary alcohols are smoothly convertible to carboxylic acids. Alde-

hydes are oxidized to carboxylic acids even in the absence of metallic catalysts. Various olefins are epoxidized with aqueous H_2O_2 and a Na_2WO_4–phosphonic acid–$Q^+HSO_4^-$ ternary catalyst system. Sulfides are oxidized to sulfoxides or sulfones under the biphasic conditions. These methods are high-yielding, clean, safe, operationally simple, and cost-effective. The utility of the succinct olefin- and alcohol-oxidation methods has been highlighted by their application to the direct conversion of cyclohexene to adipic acid. We strongly recommend that the current practices using toxic stoichiometric oxidants be replaced by these environmentally friendly catalytic processes.

Acknowledgement

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